

*Original Research Article*

# Different cytokines and Lipid Profile in Suicidal and Non Suicidal Adults with Major depression

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## Abstract

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We tested whether tumor necrosis factor-alpha, Interlukin-1 $\beta$ , and lipid profile might be associated with suicide attempts in adult patients with major depression. Plasma levels of Tumor Necrosis Factor-alpha, Interleukin-1 $\beta$ , and lipid profile were analyzed in 60 adult patients with major depression diagnosed according to DSM-IV criteria for Major depression (22 suicidal attempters and 38 patients without suicidal ideas), and 30 healthy controls. At univariate analyses, plasma level of Tumor Necrosis Factor-alpha and Triglyceride were significantly higher in suicide attempters and non-suicidal attempter depressed patients than those of healthy control (all  $p < 0.05$ ), while the plasma level of Total Cholesterol and Low density lipoprotein among suicide attempters were significantly lower than those non-suicidal attempter depressed patients or healthy control subjects ( $p < 0.05$ ). With exception of TC and LDL, the results of the study do not concomitant with the supposition that pro inflammatory cytokines and lipids levels are associated with suicide attempts in adults with major depression. The effective biological markers identification in suicidal attempters still represents a challenge for future research.

**Keywords:** Cytokine, Depression, Inflammation, Lipid, Suicide.

## INTRODUCTION

Suicide is a substantial public health concern and one of the commonest cause of death throughout the world(1). In Iraq, the suicide rate is a current health problem exacerbated by the fact that it is a country suffered war and destruction in all fields of life. Although most of Iraqi people are Muslim and Islam forbids suicide, it has exhibited an expansion in its suicide rate. For instant, between 2015 and 2018 there was an elevation in the suicide risk from 1.09/105 to 3/105 populations(2). This is a worrying and alarming phenomenon need to strategies of prevention.

The causes of suicidal behavior are seem to be associated with different psychological, environmental and genetic factors. Recently, immune response blamed in suicidal behavior via the activity of cytokines, that trigger complex brain capacities when they transmitted

through blood brain barrier (3).

Evidence of such attributed etiology arises from both human and animal models studies, as a systematically administration of pro-inflammatory cytokines induce behavioral complex that is known as "sickness behavior". This behavioral syndrome manifests as the elevated body temperature, decreased appetite and sensitivity to positive stimuli, as well as reduced social interaction and general activity, which closely resembles depressive symptoms(4).

Recent meta-analysis link a pro-inflammatory cytokines with events-related suicide, including increased levels of Interleukin (IL)-6, decreased levels of IL-2, and increased levels of Tumor Necrosis Factor-alpha (TNF- $\alpha$ )(5). Supporting these key observations, another novel meta-analysis on role of inflammation in suicide

concluded that the increased level of IL-1 $\beta$  was most robustly associated with suicidal attempts, and this cytokine may help discriminate non-suicidal from suicidal patients (6). In contrast, previous researches that have examined circulatory cytokines in suicidal patients with major depression (MD) did not find any statistically significant difference in TNF- $\alpha$  level (7) and IL-1 $\beta$  level (3) in compared to non-suicidal patients with MD. Postmortem researches found that levels of TNF- $\alpha$ , and IL-1 $\beta$  were elevated at both the messenger RNA and protein levels in the Brodmann area 10 (anterior prefrontal cortex) of teenage suicide victims (8).

Additionally, suicidal patients with MD tend to have dysregulation of the lipids than non-suicidal depressed patients (1). Lipid mediators are essential endogenous controllers of neural cell multiplication, differentiation, inflammation, oxidative stress, and programmed cell death (9). Some human studies have considered a possible connection between lower levels of TC and suicidality (10-14), others studies have shown no relationship between suicide and lipid parameters (15-18).

Besides TC, other researches have investigated the link between Triglyceride (TG), Low density lipoprotein (LDL), High density lipoprotein (HDL), depression, and suicidality (11, 18). Some researchers have documented that low level of TG was significantly related with suicidal tendency in depressed patients (11). However, for LDL or HDL, Cantarielli et al. did not find any difference between suicide and non suicide patients with major depression (11). Because of the conflicting results of the cytokine levels and lipid profile on suicide, we want to focus on these subjects. The aim of current study were (1) to verify whether MD patients with suicidal attempter (SA) have a similar pro-inflammatory cytokines and lipid profile to that MD patients with Non-suicidal attempter (NSA) or not.

## SUBJECTS AND METHODS

After the approval of protocol by the Ethical Review Board for human studies, faculty of nursing / university of kufa / Iraq (No. 4-04/01/2017), a case-control study was conducted in emergency departments and Psychiatric Clinic at two large teaching hospitals (Al-Sader teaching city and Al-Hakeem hospital) in Al-Najaf province, Iraq, from October 2017 to July 2018. A written informed consent was taken from each patient before enrollment in the study.

### Subjects

Details about the study participants are summarized in Table 1.

### MD patients with Suicidal Attempter (SA)

22 patients (16 male, 6 female) were enrolled on entrance to emergency departments of two large teaching hospital (Al-Sader hospital and Al-Hakeem hospital) after a failed suicide attempt. The patients ages were range from 18 to 48 years with mean of 36.91 yrs  $\pm$  10.3 SD, and body mass index (BMI) range 16-36 with mean of 25.98 kg/m<sup>2</sup>  $\pm$  6.34 SD. Suicide attempt defined according to the Center for Disease Control and Prevention as "a non-fatal, self-directed, potentially injurious behavior with an intent to die as a result of the behavior" (19).

### Control group I (MD patients with Non suicidal Attempter (NSA))

38 patients (24 men and 14 women) were recruited during the consultations in the Psychiatric Department, Al-Hakeem Hospital. The patients ages were range from 18 to 70 years with mean of 30.76 yrs  $\pm$  14.1 SD, and body mass index (BMI) range 19-33 with mean of 24.24 kg/m<sup>2</sup>  $\pm$  4.01 SD

### Control group II

Based on a clinical examination, 30 healthy subjects (13 male and 17 female) without any signs or symptoms of MD were randomly selected. Their ages were range from 20 to 67 years with mean of 31.1 yrs  $\pm$  15.4 SD, and their body mass index (BMI) range 16-35 with mean of 24.1 kg/m<sup>2</sup>  $\pm$  4.65 SD

The exclusion criteria were as follows: (1) Behaviors of patients with self-injury were determined to have no suicidal ideation or intention, any present or past major neurological or medical illness, and a current axis I comorbidity and/or comorbid personality diagnosis. (2) Patients with chronic disorders such as hepatic disorders, cardiovascular disease, hypertension, diabetes mellitus, common cold, influenza, or any other inflammation. (3) Patients who receiving anti-inflammatory, statin and/or immunosuppressive therapy. (4) Participants with a history of alcohol. Finally (5) Females with positive urine pregnancy.

### Psychiatric Diagnosis, Depression Severity and Suicidal Ideation

All study participants experienced an organized meeting by a psychiatrist and were diagnosed according to the fifth version of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Healthy subjects had no medication history (especially antidepressant drugs), familial and personal psychiatric history.

### Blood sample collection

Five ml blood sample was obtained between 7.30 and 8.00 by venous puncture from each controls after an overnight fasting period, while for SA, five ml blood sample was collected at the admission time to the emergency room after the unsuccessful attempt. The blood was set in an EDTA tube, and then plasma was separated by centrifugation at ( $3 \times 10^3$  rpm) for 20 minutes. All samples were stored at  $-80^\circ\text{C}$  until analysis.

### Pro-inflammatory cytokines

Plasma concentrations for TNF- $\alpha$  and IL-1 $\beta$  were measured by Development System of DuoSet Enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, United States) by following manufacture instructions. The detection limits for TNF- $\alpha$ , and IL-1 $\beta$  were 0.5, and  $<1$  respectively.

### Lipid profiles

Total Cholesterol and Triglycerides were measured by enzymatic CHOD-PAP and GPO-PAP calorimetric method, High density lipoprotein by accelerator selective detergent method and Low density lipoprotein by direct homogeneous enzymatic method using Architect c8000 system (Abbot Laboratories, Abbot Park, IL, USA).

### Statistical analyses

Quantitative variables were presented as mean  $\pm$  standard deviation (SD). Qualitative data were presented as proportions. By using the natural logarithms, level of the cytokines were transformed into normal distribution before statistical process. Zero cytokine levels were assigned a value consistent to 1/10 of the lowest noticeable sample in the test. To compare the demographic information between patients and control groups, the chi-squared test was used. Differences among SA, NSA, and healthy subjects (control group) were estimated using one way ANOVA for Quantitative data with an additional post-hoc test (Bonferroni Test). Data of the studied groups analyzed by using the statistical package SPSS version 20 (SPSS Inc., Illinois, United States). P-value set at  $\leq 0.05$  is considered as significant difference between study variables.

## RESULTS

### Demographic and Clinical characters of studied groups

A total of 60 patients with MD (40 men and 20 women) and 30 healthy controls (13 men and 17 women) were

included in the current study (See table 1). The patients were categorized into two groups according to suicide attempts.

### MD patients with Suicidal Attempter (SA) group

Among the patients, 22 (36.6%) had recently attempted suicide [suicide attempters (SA) vs. non-suicide attempters (NSA)], were recognized by the clinician as presenting an impending risk to self at the time of sample collection. The more frequent way of suicide attempt was medication overdose [12], followed by cutting wrists [5], drinking cleaning agents [3], and stabbing self in the abdomen [2]. Ten patients in the suicidal MD group (45.5%) were without using medication for at least 6 months. 12 patients (54.5%) been treated with one of the following drugs: citalopram, fluoxetine, lithium, sertraline, and mirtazapine for duration range from 1 month to 3 years.

### MD patients with non-suicidal attempter (NSA) group

18 of the 38 patients (47.4%) were free from medication for at least 6 months, and 20 patients (52.6%) had been treated with the following drugs: fluoxetine, lithium, sertraline, risperidone, mixed amphetamine salt and methylphenidate for duration ranging from 1 month to 2 years.

The three groups were compared in terms of age, gender, BMI, marital status, level of education, occupation, income, and residence. As shown in Table 1, the MD patients and controls did not differ significantly in any of these features except marital status, and income. Most of the SA were significantly married ( $p < 0.001$ ), and do not have enough income ( $p = 0.002$ ).

### Pro-inflammatory cytokines and lipid profile findings

Means and Standard deviations of plasma pro-inflammatory cytokines levels and lipid parameters are summarized in (Table 2). The comparative analysis of the level of TNF- $\alpha$ , IL-1 $\beta$  and lipid profile among three studied groups showed significant differences in the plasma levels of TNF- $\alpha$ , TC, LDL, and TG (all  $p < 0.05$ ). No significant difference for IL-1 $\beta$  and HDL levels were detected.

Post-hoc analysis showed that SA had increased levels of TNF- $\alpha$  compared with healthy controls ( $p < 0.001$ ). Similarly, NSA had significantly increased TNF- $\alpha$  levels ( $p < 0.001$ ) compared with healthy control. No significant difference for TNF- $\alpha$  levels was observed between SA and NSA ( $p > 0.05$ ).

Moreover, post-hoc test showed that subjects with SA presented significantly lower TC and LDL levels

**Table 1.** Demographic and Clinical characters of studied groups.

	SA n=22		NSA n=38		HC n=30		Statistics	p value
	Mean ± SD (rang)		Mean ± SD (rang)		Mean ± SD (rang)			
<b>Age</b>	36.91 ± 10.3 (18-48)		30.76 ± 14.1 (18-70)		31.1 ± 15.4 (20-67)		<b>F= 1.572</b>	<b>0.214</b>
<b>BMI</b>	25.98 ± 6.34 (16-36)		24.24 ± 4.01 (19-33)		24.1 ± 4.65 (16-35)		<b>F= 1.145</b>	<b>0.323</b>
	n	%	n	%	n	%		
Gender								
Male	16	72.7%	24	63.2%	13	43.3%	<b>χ<sup>2</sup> = 5.025</b> df = 2	0.081
Female	6	27.3%	14	36.8%	17	56.7%		
Educational level								
Not read and not write	8	36.4%	6	15.8%	7	23.3%	<b>χ<sup>2</sup> = 10.554</b> df = 6	0.104
Read and write	4	18.2%	6	15.8%	5	16.7%		
Secondary School	8	36.4%	24	63.2%	11	36.7%		
Institute \ College	2	9.1%	2	5.3%	7	23.3%		
Occupation								
Employee	2	9.1%	6	15.8%	4	13.3%	<b>χ<sup>2</sup> = 0.541</b> df = 2	0.763
Unemployed	20	90.9%	32	84.2%	26	86.7%		
Monthly Income								
Enough	6	27.3%	20	52.6%	25	83.3%	<b>χ<sup>2</sup> = 17.302</b> df = 4	0.002
Enough to some extant	6	27.3%	8	21.1%	3	10.0%		
Not enough	10	45.5%	10	26.3%	2	6.7%		
Residence								
urban	20	90.9%	30	78.9%	27	90.0%	<b>χ<sup>2</sup> = 2.333</b> df = 2	0.312
Rural	2	9.1%	8	21.1%	3	10.0%		

*Abbreviations:* SA=Suicidal attempter; NSA=Non-Suicidal attempter; HC=Healthy control; BMI=Body Mass Index; DMS-IV=Fifth version of Diagnostic and Statistical Manual of Mental Disorders; and SD=standard deviation.

**Table 2.** Mean ± Standard deviation for Levels of Plasma TNF-α, IL-1β and lipids in SA, NSA and HC.

	SA n=22	NSA n=38	HC n=30	<i>Post-hoc analysis</i>		
	Mean ± SD	Mean ± SD	Mean ± SD	Statistics	p value	
TNF-α	4.03 ± 0.71	3.77 ± 0.67	3.06 ± 0.57	F= 16.650	<0.001	SA, NSA>HC*
IL-1β	0.22 ± 0.16	0.22 ± 0.15	0.21 ± 0.15	F=0.030	0.970	
TC	155.55 ± 8.65	172.02 ± 7.71	174.07 ± 8.82	F=36.733	<0.001	SA<NSA, HC*
HDL	52.42 ± 14.07	50.27 ± 12.16	47.46 ± 12.78	F=0.982	0.379	
LDL	81.64 ± 5.91	94.43 ± 5.46	100.90 ± 4.86	F=110.982	<0.001	SA<NSA, HC*
TG	166.19 ± 36.77	175.98 ± 29.13	140.90 ± 37.35	F=9.185	<0.001	SA, NSA>HC*

*Abbreviations:* \* =The Bonferroni statistical way was used for *post hoc* comparisons; SA=Suicidal attempter; NSA=Non-Suicidal attempter; HC=Healthy control; TNF-α=Tumor Necrosis Factor-alpha; IL-1β= Interleukin-1 beta; TC=Total Cholesterol; LDL=Low Density Lipoprotein; HDL= High Density Lipoprotein; TG=Triglycerides; and SD=standard deviation.

compared with NSA (all  $p < 0.001$ ). Similarly, MD patients with suicide attempt had significantly lower TC and LDL levels in comparison to control group (all  $p < 0.001$ ).

No statistical difference for TC and LDL levels were detected between NSA and normal control (all  $p > 0.05$ ).

Furthermore, TG level was significantly higher in both SA and NSA ( $p = 0.009$  and  $p < 0.001$  respectively) in comparison with healthy control. No significant difference for TG level was observed between SA and NSA ( $p > 0.05$ ).

## DISCUSSION

We measured two pro-inflammatory cytokines and lipid

profile in plasma of healthy control subjects, non-suicide major depressive disorder and suicide attempters with well-defined clinical psychiatric profiles. In this study, while the level of TNF-α was significantly higher in suicide attempters and non-suicidal patients with major depression (MD) than those of healthy control, the levels of TC and LDL among suicide attempters were significantly lower than those among non-suicidal depressed patients or healthy control subjects. Other studied parameters did not show any statistically significant differences among study groups.

Our finding of increased plasma level of TNF-α in suicidal depressed patients in comparison to healthy subjects were in agreement with several previous studies that analyze cytokines in suicidal adult patients compared

to healthy (20-22). However, we found that TNF- $\alpha$  level also elevated in non-suicidal MD patients but this consistent with many adult MD studies (3, 23, 24), so it seems that elevated plasma level of TNF- $\alpha$  may be related to MD rather than suicide. The results of previous researches of the TNF- $\alpha$  and IL-1 $\beta$  levels in plasma and CSF in MD patients with suicidality were contradictory (25). Some authors reported a significant elevation of TNF- $\alpha$  (26-28), and IL-1 $\beta$  (25, 29, 30) levels in suicidal attempters, while others did not mention such difference in the TNF- $\alpha$  (7, 31-35), and IL-1 $\beta$  (3) concentrations between suicidal attempters and non-suicidal depressed patients. To our knowledge, lower levels were found in only one study for TNF- $\alpha$  (3) when compared the suicidal patients with non-suicidal depressed patients.

In line with cytokines, the current study found that IL-1 $\beta$  level was not associated with depressive symptom and suicidality, that consistent with a previous study showed no significant difference in IL-1 $\beta$  level between MD patients and healthy controls, and concluded that IL-1 $\beta$  level might play an essential role in the psychopathology of acute-phase MD (36). These differences may come from using different immunoassay techniques (37) and different plasma storage conditions. A recent report demonstrated that storage of sera at -80°C and  $\leq$  130°C for up to 3 months does not cause substantial changes in cytokines concentration, while storage at 4°C and -20°C cause decrease in concentration (38).

One of the biological hypothesis that clarify the relation between inflammation and MD is the presence of an enzyme called "indoleamine 2,3-dioxygenase (IDO)" that produced in response to inflammatory stimuli, IDO catabolizes tryptophan (TRP) to kynurenine Acid (KYNA), which is then transformed into production of serotonin (5-HT, neuroactive metabolites). Both MD and suicidality have been connected to low 5-HT function, suggesting that activation of IDO may be linked to the depression rather than to the suicidality (6, 8).

Our second findings of decreased levels of TC and LDL in SA compared to NSA or healthy control subjects were consistent with a recent study (1), as well as, in agreement with the determinations of a meta-analysis study, which published in 2015 and involved 65 articles, revealed an association between lower levels of TC and LDL with suicidality (12). However, other reports did not find a relationship between plasma TC, LDL and suicidal behavior (15, 39).

With respect to triglyceride levels, the current study determined high TG level in SA and NSA with MD. These results agree with previous reported finding that reveal a significant association between triglyceride levels and depression (1), but not with other reports that observed low TG level in participants with suicidal behavior (11). However, other researchers found conflicting results (40).

The mechanism that may link between low TC and LDL with suicide in depressed individuals is unclear. It has been established that approximately all cholesterol molecules formed inside the brain by de novo synthesis and blood-brain barrier ensure a selective inhibition of its uptake from the blood circulation (41).

However, it is workable that low cholesterol level in peripheral circulation in those patients with MD occurs concurrently with cholesterol alterations that occur in distinct synaptic lipid rafts in neurons. So, this lead to decrease in serotonergic communication activity, and consequently, cause violent suicidal attempts and instinctive responses (1). Another hypothesis is that lipid rafts be membrane domains where stimulated by a group of receptors signaling from a neurotransmitter, such as serotonin 1A (5-HT<sub>1A</sub>) receptor (42). As consequence of low lipid micro viscosity in neural membranes, 5-HT<sub>1A</sub> receptor exposure on the membrane surface will be decreased, with hypo function of such receptors.

The present findings of two studied pro inflammatory cytokines and lipid profile dysregulation ought to be viewed as preparatory in light of many limiting factors: First of the all, the small size of the sample limits causal conclusions in regards to the correlation between inflammation and suicidality. Second- MD Patients in current study were doctor's facility in-patients get upper and other psychotropic medicines and a few members were utilizing calming pharmaceuticals, all of which could have impacted levels of our needy factors (43). Finally, the watched assemble distinction in pro inflammatory cytokines between patients with high versus bring down levels of inflammation seemed autonomous of suicidal ideation in current study.

## CONCLUSIONS

With exception of TC and LDL, the results of the study not concomitant with the supposition that pro inflammatory cytokines and lipids levels are associated with suicide attempts in adults with major depression. The effective biological markers identification in suicidal attempters still represents a challenge for future research.

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